A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on August 17, 2010 has been entered.

Claims 15-28 are pending wherein the subject matter under consideration are those methods of treatment drawn to inhibiting transient lower esophageal sphincter relaxations (TLESRs), treating GERD, inhibiting reflux of gastric juice and treating regurgitation of gastric juice comprising administering the elected metabotropic glutamate receptor 5 (mGluR5) antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP). The election was made on June 18, 2007. The search was extended to include 3-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]-5-(methoxymethyl)benzonitrile and 3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile, claims 15-18 and 24-28.

Those methods drawn to other treatments, claims 19-23, remain withdrawn from consideration by the Examiner, as drawn to non-elected inventions, 37 CFR 1.142(b).

An Information Disclosure Statement filed August 17, 2010 is acknowledged and has been reviewed.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention. The claims are broadly directed to inhibiting transient lower esophageal sphincter relaxations (TLESRs), treating gastroesophageal reflux disease (GERD), inhibiting reflux of gastric juice and treating regurgitation of gastric juice comprising administering a metabotropic glutamate receptor 5 antagonist. The specification discloses three individual examples for compounds having the required mGluR5 antagonistic activity. The metabotropic glutamate receptor 5 antagonists MPEP and 3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile, disclosed in Examples 1-3, pages 10-13 of the specification, are shown to inhibit lower esophageal sphincter relaxations by a percentage.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 where the court set forth factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to therapeutic modalities for pathologies of the lower esophageal sphincter. The recited species that are characterized as metabotropic glutamate receptor 5 antagonists are 2-methyl-6-(phenylethynyl)-pyridine (MPEP), 3-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]-5-(methoxymethyl)benzonitrile and 3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile. The relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in the area of gastroenterology.

The breadth of the claims

The claims are very broad in terms of the structurally diverse compounds encompassed in the language of the claims, i.e., metabotropic glutamate receptor 5 antagonists. No structure-activity relationship is provided, nor is there any guidance that would assist the skilled artisan in finding additional metabotropic glutamate receptor

5 antagonists. The genus of claimed compounds is so broad as to present an undue burden.

The amount of direction or guidance provided and the presence or absence of working examples

The working examples are limited to the administration of two metabotropic glutamate receptor 5 antagonists. No guidance is specifically directed to either reflux or regurgitation. Passages from The Merck Index that were previously provided show various and unrelated etiologic factors that may cause or be the result of TLESRs. Most fundamentally, GERD is the result of incompetence of the lower esophageal sphincter. However, variations in intrinsic sphincter pressure, the presence or absence of an inflammatory process, the angle of the cardioesophageal junction, the action of the diaphragm, the effect of gravity, the volume of gastric contents, local mucosal protective functions and the general health status of the patient must be considered. It is unclear whether or not functional vomiting is encompassed in the present claim language. As required by instant claim 18, a nexus between inhibition of TLESRs and a condition of passively spitting up gastric contents is absent. Further, it is unclear whether conditions of psychogenic vomiting and a correlation to inhibition of TLESRs are contemplated by the present claim language.

The quantity of experimentation necessary

The claims encompass all compounds exhibiting metabotropic glutamate receptor 5 antagonism. However, the disclosure only presents a limited number of compounds. Applicants have failed to provide guidance as to which particular

compound would be preferred for treating reflux or regurgitation comprising administering a particular metabotropic glutamate receptor 5 antagonist. The skilled artisan would expect the interaction of a particular compound in a therapeutic regimen to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for each agent especially considering the diverse functionalities of the compounds of the instant claims. The instant specification sets forth no such understanding. Absent reasonable *a priori* expectations of success for using any particular agent characterized as a metabotropic glutamate receptor 5 antagonist based solely on receptor affinity, one skilled in the gastroenterology art would have to test extensively many compounds to discover which proves efficacious for treating reflux regurgitation, for example. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

Considering the state of the art, the high unpredictability of efficacy of any compound characterized as an antagonist of metabotropic glutamate receptor 5, based on diverse functionalities imparting different chemical and physical properties, and the lack of guidance provided by the specification, one of ordinary skill in the gastroenterology art would be burdened with undue experimentation. A meaningful search covering the entire scope of compounds is impossible.

Claims 15-18 and 28 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. In the instant case, the claims recite inhibiting transient lower esophageal sphincter relaxations (TLESRs), treating GERD, treating reflux of gastric juice, treating regurgitation comprising administering any metabotropic glutamate receptor 5 antagonist.

There is insufficient written basis for the instant, broadly claimed subject matter. This is a Written Description rejection.

M.P.E.P. § 2163 states, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention...one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

While the Tables on page 11 demonstrate a percent inhibition of TLESRs in an animal model, there is inadequate written disclosure directed to various pathologies that are characterized by “reflux,” that may or may not be of a gastroesophageal origin, “regurgitation,” that may or may not be limited to a pediatric population, and transient lower esophageal sphincter relaxations, which the prior art recognizes as caused by

unrelated, or etiologically distinct, factors, wherein a reasonable number of metabotropic glutamate receptor 5 antagonists are described to support the claimed genus. Applicants have not conveyed possession of the invention with reasonable clarity to one skilled in the art, particularly with respect to dosing regimens that would be required as, particularly, in the case of regurgitation in an infant, or in the case of psychogenic vomiting. The disclosure lacks sufficient written description for all claimed limitations. No working examples are provided that would describe to one of ordinary skill in the art an embodiment that meets all the limitations of the claims. Sufficient guidance to support predictable operability of the invention to one of ordinary skill in the art is absent.

Claims 24-27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Favorable consideration would be given to a claim drawn to the treatment of GERD comprising administering 2-methyl-6-(phenylethynyl)-pyridine (MPEP), 3-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]-5-(methoxymethyl)benzonitrile or 3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached on 10:30 AM-7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel, can be reached on 591-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 26, 2010

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614